PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/00 — A1

(11) International Publication Number: **WO 97/47292**

(43) International Publication Date: 18 December 1997 (18.12.97)

(21) International Application Number: PCT/US97/09977

(22) International Filing Date: 10 June 1997 (10.06.97)

(30) Priority Data:
08/662,389 12 June 1996 (12.06.96) US

(71) Applicant: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US).

(72) Inventor: SINGER, Robert, Ernest, Jr.; 3 Kingsmount Court, Fairfield, OH 45014 (US).

(74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217 (US).

(81) Designated States: AU, BR, CA, CN, JP, KR, MX, SG, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: USE OF H_2-ANTAGONISTS FOR THE MANUFACTURE OF A TOPICAL COMPOSITION FOR THE TREATMENT OF COLDS

(57) Abstract

Oral compositions for topical application containing an H_2 antagonist to provide protection against colds and flu.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

USE OF H_2-ANTAGONISTS FOR THE MANUFACTURE OF A TOPICAL COMPOSITION FOR THE TREATMENT OF COLDS

TECHNICAL FIELD

The present invention relates to a method of preventing or controlling colds and similar maladies, such as flu, through the use of an oral composition containing an H_2 blocker applied to the gingival or oral mucosal tissue of the subject susceptible to colds.

BACKGROUND OF THE INVENTION

The common cold, although not usually a serious illness, is a highly prevalent, discomforting and annoying infliction. The term "common cold" is applied to minor respiratory illnesses caused by a variety of different respiratory viruses. While rhinoviruses are the major known cause of common colds, accounting for approximately 30 percent of colds in adults, viruses in several other groups are also important. While immune responses occur, and infection with some respiratory tract viruses therefore could be prevented by a vaccine, development of a polytypic vaccine to cover all possible agents is impractical. Thus, the problem of controlling acute upper respiratory disease presents complex challenges, and the long-desired discovery of a single cure for the common cold is an unrealistic expectation.

With rhinovirus infection, symptoms of nasal discharge, nasal congestion, and sneezing usually commence on the first day of illness and progress to maximum severity by the second or third day. The costs of treating colds with over-the-counter medications in the United States is estimated at an annual cost of over 1.5 billion dollars. The direct costs of treatment in outpatient clinics is estimated at almost four billion dollars. Indirect costs, based on the amount of loss in wages because of restricted activity are substantially higher.

At present, only symptomatic treatment is available for the common cold; the majority of these drugs are taken orally. Exemplary prior art oral compositions for treatment of nasal and other cold, flu, allergy and sinus symptoms and the discomfort, pain, fever and general malaise associated therewith generally contain an analgesic (aspirin or acetaminophen) and one or more antihistamines, decongestants, cough suppressants, antitussives and expectorants. Other specific pharmaceutical actives for nasal symptoms (e.g., congestion) generally contain either oxymetazoline or phenylephrine. These actives are generally delivered topically to the nasal muc sa via a nasal spray. For individuals with certain medical conditions such as heart disease, hypertension, diabetes or thyroid disorders, oral

drugs such as decongestants could pose a risk of unfavorable drug interactions and may cause an adverse reaction. It would, therefore, be highly desirable to deliver relief from specific nasal symptoms via compositions without the need for such pharmaceutical actives.

It has been discovered that topical application of an H_2 antagonist compound to the gingival or oral mucosal tissues of a subject susceptible to colds and/or flu helps to reduce the incidence of such maladies.

It is therefore an object of the present invention to provide topical oral compositions which provide treatment to prevent colds and flu.

SUMMARY OF THE INVENTION

The present invention relates to a method of reducing colds and cold-like symptoms, such as flu, in subjects susceptible to such maladies by applying a composition containing an effective amount of an H_2 antagonist compound to the gingival or oral mucosal tissues.

DETAILED DESCRIPTION OF INVENTION

The compositions of the present invention contain certain essential components as well as non-essential components.

H_2 Antagonist Compound

The H_2 antagonist compounds useful in the present invention include many different agents. U.S. Patent 5,294,433, March 15, 1994, to Singer, et al., incorporated herein by reference in its entirety, discloses many different H_2 antagonist compounds.

Preferred H_2 antagonists include cimetidine, etintidine, ranitidine, ICIA-5165, tiotidine, ORF-17578, luptidine, donetidine, famotidine, roxatidine, pifatidine, lamtidine, BL-6548, BMY-25271, zaltidine, nizatidine, mifentidine, BMY-52368, SKF-94482, BL-6341A, ICI-162846, ramixotidine, Wy-45727, SR-58042, BMY-25405, loxtidine, DA-4634, bisfentidine, sufotidine, ebrotidine, HE-30-256, D-16637, FRG-8813, FRG-8701, impromidine, L-643728, and HB-4-08.

Cimetidine, ranitidine, famotidine, roxatidine, nizatidine, and mifentidine are more preferred and cimetidine and ranitidine are most preferred.

H_2 antagonist compounds are used in an amount of from about 0.001% to about 40%, preferably from about 0.01% to about 20%, most preferably from about 0.1% to about 10%.

Acceptable Carrier

The carrier for the active component(s) can be any vehicle suitable for use in the oral cavity. Such carriers include the usual components of mouthwashes, toothpastes, tooth powders, prophylaxis pastes, lozenges, gums and the like and are

more fully described hereinafter. Dentifrices and mouthwashes are the preferred systems.

In addition to the active agent(s), the present compositions may contain antiplaque/gingivitis agent such as quaternary ammonium compounds, water insoluble agents such as triclosan, teas, as defined herein later, stannous salts and zinc salts. These types of agents are described in U.S. patent 4,894,220; January 16, 1990 to Nabi et al, U.S. Patent 4,656,031, April 7, 1987 to Lane et al; and U.S. Patent 5,004,597, April 2, 1991 to Majeti et al. All incorporated herein by reference in their entirety.

The abrasive polishing material contemplated for use in the present invention can be any material which does not excessively abrade dentin. These include, for example, silicas including gels and precipitates, calcium carbonate, dicalcium orthophosphate dihydrate, calcium pyrophosphate, tricalcium phosphate, calcium polymetaphosphate, insoluble sodium polymetaphosphate, hydrated alumina, and resinous abrasive materials such as particulate condensation products of urea and formaldehyde, and other such as disclosed by Cooley et al. in U.S. Patent 3,070,510, December 25, 1962, incorporated herein by reference. Mixtures of abrasives may also be used.

Silica dental abrasives, of various types, can provide the unique benefits of exceptional dental cleaning and polishing performance without unduly abrading tooth enamel or dentin. Silica abrasive materials are also exceptionally compatible with sources of soluble fluoride and polyphosphonates. For these reasons they are preferred for use herein.

The silica abrasive polishing materials useful herein, as well as the other abrasives, generally have an average particle size ranging between about 0.1 to 30 microns, preferably 5 and 15 microns. The silica abrasive can be precipitated silica or silica gels such as the silica xerogels described in Pader et al., U.S. Patent No. 3,538,230, issued March 2, 1970 and DiGiulio, U.S. Patent No. 3,862,307, June 21, 1975, both incorporated herein by reference. Preferred are the silica xerogels marketed under the tradename "Syloid" by the W. R. Grace & Company, Davison Chemical Division. Preferred precipitated silica materials include those marketed by the J. M. Huber Corporation under the tradename, "Zeodent", particularly the silica carrying the designation "Zeodent 119". These silica abrasives are described in U.S. Patent No. 4,340,583, July 29, 1982, incorporated herein by reference.

The abrasive in the compositions described herein is present at a level of from about 6% to about 70%, preferably from about 15% to about 25% when the dentifrice is a toothpaste. Higher levels, as high as 90%, may be used if the

composition is a toothpowder.

Flavoring agents can also be added to dentifrice compositions. Suitable flavoring agents include, among many others, oil of wintergreen, oil of peppermint, oil of spearmint, and oil of clove. Sweetening agents which can be used include aspartame, acesulfame, saccharin, dextrose, levulose and sodium cyclamate. Flavoring and sweetening agents are generally used in dentifrices at levels of from about 0.005% to about 2% by weight.

Dentifrice compositions can also contain emulsifying agents. Suitable emulsifying agents are those which are reasonably stable and foam throughout a wide pH range, including nonsoap anionic, nonionic, cationic, zwitterionic and amphoteric organic synthetic detergents. Many of these suitable surfactants are disclosed by Gieske et al. in U.S. Patent No. 4,051,234, September 27, 1977, incorporated herein in its entirety by reference.

Water is also present in the toothpastes of this invention. Water employed in the preparation of commercially suitable toothpastes should preferably be deionized and free of organic impurities. Water generally comprises from about 10% to 50%, preferably from about 20% to 40%, by weight of the toothpaste compositions herein. These amounts of water include the free water which is added plus that which is introduced with other materials such as with sorbitol.

In preparing toothpastes, it is necessary to add some thickening material to provide a desirable consistency. Preferred thickening agents are carboxyvinyl polymers of the type mentioned previously herein, xanthan gum, carrageenan, hydroxyethyl cellulose and water soluble salts of cellulose ethers such as sodium carboxymethyl cellulose and sodium carboxymethyl hydroxyethyl cellulose. Natural gums such as gum karaya, gum arabic, and gum tragacanth can also be used. Colloidal magnesium aluminum silicate or finely divided silica can be used as part of the thickening agent to further improve texture. Thickening agents in an amount from 0.5% to 5.0% by weight of the total composition can be used.

It is also desirable to include some humectant material in a toothpaste to keep it from hardening. Suitable humectants include glycerin, sorbitol, and other edible polyhydric alcohols at a level of from about 15% to about 70%.

Another preferred embodiment of the present invention is a mouthwash composition. Conventional mouthwash composition components can comprise the carrier for the activ agents of the present invention. Mouthwashes generally comprise from about 20:1 to about 2:1 of a water/ethyl alcohol solution and preferably other ingredients such as flavor, sweeteners, humectants and sudsing agents such as those mentioned above for dentifrices. The humectants, such as

glycerin and sorbitol give a moist feel to the mouth. Generally, on a weight basis the mouthwashes of the invention comprise 0% to 60% (preferably 10% to 25%) ethyl alcohol, 0% to 20% (preferably 5% to 20%) of a humectant, 0% to 2% (preferably 0.01% to 0.15%) emulsifying agent, 0% to 0.5% (preferably 0.005% to 0.06%) sweetening agent such as saccharin, 0% to 0.3% (preferably 0.03% to 0.3%) flavoring agent, and the balance water.

Suitable lozenge and chewing gum components are disclosed in U.S. Patent No. 4,083,955, April 11, 1978 to Grabenstetter et al., incorporated herein by reference.

Other optional components useful in the present invention are pyrophosphate salts such as those described in U.S. 4,515,772, May 7, 1985 to Parran et al. incorporated herein by reference. Also useful are nonionic antimicrobials such as triclosan described in U.S. 4,894,220, January 16, 1990 to Nabi et al. Both patents are incorporated herein by reference.

Another agent which can be used in the present compositions is an alkali metal bicarbonate, such as sodium bicarbonate. These are stable items of commerce and can be used together with a peroxide compound in separate compartments such as disclosed in U.S. 4,849,213 and U.S. 4,528,180, both to Schaeffer, incorporated herein by reference in its entirety.

Other preferred compositions of the subject invention are controlled-release drug delivery systems for placement in the periodontal pocket. Such systems include, but are not limited to, the cellulose hollow fibers disclosed in U.S. Pat. No. 4,175,326, issued to Goodson on Nov. 27, 1979; the ethylcellulose films disclosed in U.S. Pat. No. 4,568,535 issued to Loesche on Feb. 4, 1986; the absorbable putty-like material disclosed in U.S. Pat. No. 4,568,536 issued to Kronenthal, Maftei and Levy on Feb. 4, 1986; the biodegradable microspheres and matrix disclosed in U.S. Pat. No. 4,685,883 issued to Jernberg on Aug. 11, 1987; the microparticle or microcapsule suspensions disclosed in U.S. Pat. No. 4,780,320 issued to Baker on Oct. 25, 1988; the polymeric devices disclosed in European Patent Applicatin No. 0,140,766 of Goodson, published May 8, 1985; and the lactide/glycolide executions described in U.S. Patent No. 5,198,220, March 30, 1993 to Damani; these patents are incorporated herein by reference. Such controlled-release delivery systems generally include a solid matrix, usually of polymeric material, loaded with one or more active agents, the matrix entrapping the H_2 antagonists. Typically, the active agents diffuse from the wolid material into the periodontal pocket over time.

Preferred controlled-release drug delivery systems comprise from about 0.001% to about 50%, more preferably from about 0.01% to about 25%, more

preferably still from about 0.1% to about 15%, still more preferably from about 1% to about 10%, of a H_2 antagonist and a controlled-release carrier.

The pH of the present compositions and/or its pH in the mouth can be any pH which is safe for the mouth's hard and soft tissues. Such pH's are generally from about 3 to about 10, preferably from about 5 to about 9.

METHOD OF MANUFACTURE

The carrier compositions of the present invention can be made using methods which are common in the oral products area.

For example, toothpaste compositions may be prepared by mixing part of the humectant and water together and heating to 66°-71°C. The fluoride source, if present, is then added along with the sweetener, the opacifier and the flavor. The cranberry extract may be combined with the glycerine prior to adding to the other components.

COMPOSITIONS OF USE

The present invention in its method aspect involves applying to the gingival and/or oral mucosal tissue safe and effective amounts of the compositions. Generally an amount of at least about 5 grams of a mouthwash and at least about 0.5 of a toothpaste or liquid dentifrice.

A preferred method of the subject invention involves the contact of a composition of the subject invention with oral cavity soft tissue afflicted with gingivitis or periodontitis for at least about 15 seconds, preferably from about 20 seconds to about 10 minutes, more preferably from about 30 seconds to about 60 seconds. The method often involves expectoration of most of the composition following such contact, preferably followed by rinsing, e.g., with water. The frequency of such contact is preferably from about once per week to about four times per day, more preferably from about thrice per week to about thrice per day, more preferably still from about once per day to about twice per day. The period of such treatment typically ranges from about one day to a lifetime.

The following examples further describe and demonstrate preferred embodiments within the scope of the present invention. The examples are given solely for illustration and are not to be construed as limitations of this invention as many variations thereof are possible without departing from the spirit and scope thereof.

EXAMPLES 1 AND 2

Examples of toothpaste and tooth gel compositi ns of the subject invention are made by conventional processes by mixing the following:

Ingredients	Example 1 (Wt. %)	Example 2 (Wt. %)
Sorbitol	41.44	35.00
Saccharin Sodium	0.46	0.20
FD&C Blue (1% soln)	--	0.05
Precipitated Silica	20.00	25.00
Sodium Fluoride	0.24	0.24
Flavor	1.00	1.50
Purified Water	q.s.	q.s.
Sodium Alkly Sulfate	4.00	1.20
Trisodium Phosphate	1.45	--
Monosodium Phosphate	0.59	--
Carbopol 940	0.30	0.25
Xanthan Gum	0.48	0.65
Titanium Dioxide	0.53	--
Cimetidine	2.00	--
Mifentidine	--	0.50

EXAMPLES 3 AND 4

Examples of mouthwash compositions of the subject invention are made by conventional processes by mixing the following:

Ingredients	Example 3 (Wt. %)	Example 4 (Wt. %)
Sorbitol	37.20	37.20
Glycerin	19.00	19.00
Polyethylene Glycol 600	3.00	3.00
Sodium Saccharin	0.17	0.17
Precipitated Silica	20.00	20.00
Sodium Fluoride	0.24	0.24
Flavor	0.90	0.90
Purified Water	q.s.	q.s.
Sodium Alkly Sulfate	1.00	1.00
Monobasic Sodium Phosphate, Monohydrate	5.00	5.00
Fumed Silica	2.00	2.00
Carboxymethylcellulose	0.30	0.30
Titanium Dioxide	0.50	0.50
Famotidine	2.50	--
Nizatidine	--	4.00

EXAMPLES 5 AND 6

Examples of toothpaste and tooth gel compositions of the subject invention are made by conventional processes by mixing the following:

Ingredients	Example 5 (Wt. %)	Example 6 (Wt. %)
Sorbitol	17.23	17.23
Silica	23.41	23.41
Sodium Alkyl Sulfate	4.00	4.00
Xanthan Gum	0.60	0.60
Titanium Dioxide	0.50	--
Carbopol 940	0.20	0.20
Glycerin	9.00	9.00
Sodium Fluoride	0.24	0.24
Tetrapotassium Pyrophosphate	6.38	6.38
Sodium Acid Pyrophosphate	2.10	2.10
Tetrasodium Pyrophosphate	2.05	2.05
Polyethylene Glycol 600	3.00	3.00
Peppermint Oil	0.80	--
Spearmint Oil	--	1.00
Saccharin Sodium	0.46	0.46
FD&C Blue (1% soln)	0.05	0.05
Cimetidine	--	1.00
Ranitidine	2.00	--

EXAMPLES 7 AND 8

Examples of mouthwash compositions of the subject invention are made by conventional processes by mixing the following:

Ingredients	Example 7 (Wt. %)	Example 8 (Wt. %)
Cetylpyridinium Chloride	0.045	0.045
Domiphen Bromide	0.005	0.005
Purified Water	q.s.	q.s.
Alcohol (Standard Denatured No. 40)		
Glycerin	10.00	7.50
Poloxamer 407	0.20	0.20
Sodium Hydroxide	0.003	0.003
Sodium Benzoate	0.05	0.54
Benzoic Acid	0.005	0.003
Tween 80	0.03	0.12
FD&C Green (1% soln)	0.04	0.12
FD&C Blue (1% soln)	0.003	--

FD&C Yellow (1% soln)	--	0.001
Saccharin	0.06	0.08
Peppermint Oil	0.14	--
Spearmint Oil	--	0.12
Cimetidine	0.30	--
Ranitidine	--	0.20

EXAMPLES 9 AND 10

Examples of mouthwash compositions of the subject invention are made by conventional processes by mixing the following:

Ingredients	Example 9 (Wt. %)	Example 10 (Wt. %)
Famotidine	0.05	--
Roxatidine Acetate	--	1.0
Ethanol	12.00	15.00
Glycerin	10.00	12.00
Dibasic Sodium Phosphate Heptahydrate	0.07	0.48
Saccharin Sodium	0.08	0.08
Monobasic Sodium Phosphate Monohydrate	2.03	1.82
Polysorbate 80	0.33	0.33
FD&C Blue (1% soln)	0.02	0.02
Flavor	0.15	0.15
Purified Water	q.s.	q.s.

EXAMPLE 11

An example of a dental solution of the subject invention is made by mixing the following:

Ingredients	Example 11 (Wt. %)
Water	q.s.
Ranitidine	1.00
Flavor	0.10
Polysorbate 80	0.25
Saccharin Sodium	0.05
Methylparaben	0.20
Propylparaben	0.10

EXAMPLE 12

An example of an oral composition of the subject invention is made by mixing the following:

Ingredients	Example 12 (Wt. %)
Hydroxyethyl Cellulose	2.50
Purified Water	q.s.
Sodium Fluoride	0.09
Saccharin Sodium	0.05
FD&C Green No. 3 (1% soln)	0.01
Ranitidine	1.00

EXAMPLE 13

An example of a controlled-release polymer composition for placement in a periodontal pocket is as follows:

Ingredients	Example 13 (Wt. %)
Ethyl Cellulose, Type N22 from Hercules, Inc.	90
Mifentidine	10

The ethyl cellulose is dissolved in chloroform and then the mifentidine is added. The resulting mixture is cast on a glass plate. After evaporation of the chloroform, the residual film is removed from the plate and cut into pieces.

EXAMPLE 14

An example of a putty-like controlled-release composition for placement in a periodontal pocket is made by mixing the following:

Ingredients	Example 14 (Wt. %)
Calcium Stearate	40
Dextran	29
Castor Oil	28
Nizatidine	3

WHAT IS CLAIMED IS:

1. The use of an H_2 antagonist compound for the manufacture of a topical composition for the treatment of reducing the incidence of colds and similar maladies.

2. The use according to Claim 1 wherein the said compound is selected from the group consisting of cimetidine, etintidine, ranitidine, ICIA-5165, tiotidine, ORF-17578, luptidine, donetidine, famotidine, roxatidine, pifatidine, lamtidine, BL-6548, BMY-25271, zaltidine, nizatidine, mifentidine, BMY-52368, SKF-94482, BL-6341A, ICI-162846, ramixotidine, Wy-45727, SR-58042, BMY-25405, loxtidine, DA-4634, bisfentidine, sufotidine, ebrotidine, HE-30-256, D-16637, FRG-8813, FRG-8701, impromidine, L-643728, and HB-4-08.

3. The use according to Claim 1 or 2 wherein the said compound is selected from the group consisting of cimetidine, ranitidine, famotidine, and nizatidine and mifentidine.

4. The use according to any of Claims 1-3 wherein the said compound is selected from the group consisting of cimetidine, ranitidine, famotidine, and nizatidine.

5. The use according to any of Claims1-4 wherein the said compound is cimetidine.

6. The use according to Claim 4 wherein the said compound is ranitidine.

7. The use according to any of Claims 1-6 wherein the composition comprises 0.01% to 10% of the said compound.

8. The use according to any of Claims 1-7 wherein said composition is in the form of a toothpaste or a mouthrinse.

9. The use according to any of Claims 1-7 wherein said composition is in the form of a site specific delivery system comprised of a copolymer of lactide and glycolide.

INTERNATIONAL SEARCH REPORT

Internat. ial Application No
PCT/US 97/09977

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
—

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 4 749 700 A (JEFFREY WENIG) 7 June 1988 see column 1, line 18 - line 51 see column 4, line 3 - line 5 see column 4, line 50 - column 5, line 25 ---	1-6 7-9
X Y	US 5 373 022 A (FAWZI ET AL.) 13 December 1994 see column 5, line 9 - line 28 ---	1-6 7-9
Y	US 5 294 433 A (SINGER ET AL.) 15 March 1994 cited in the application see column 15, line 8 - line 63 see column 20, line 49 - column 21, line 8; claims 1-8 -----	7-9

☐ Further documents are listed in the continuation of box C

[X] Patent family members are listed in annex

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 October 1997	22. 10. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,	Tzschoppe, D

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat ional Application No
PCT/US 97/09977

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4749700 A	07-06-88	AU 596741 B	10-05-90
		AU 1506188 A	01-09-88
		AU 5063885 A	15-05-86
		BR 8507008 A	06-01-87
		CA 1265056 A	30-01-90
		DE 3585952 A	04-06-92
		EP 0201537 A	20-11-86
		JP 7010771 B	08-02-95
		JP 62500589 T	12-03-87
		WO 8602553 A	09-05-86
US 5373022 A	13-12-94	US 5385941 A	31-01-95
		AU 1252692 A	06-10-92
		CA 2104684 A	05-09-92
		EP 0574424 A	22-12-93
		JP 6506198 T	14-07-94
		MX 9200920 A	01-09-92
		WO 9215332 A	17-09-92
US 5294433 A	15-03-94	AU 3930493 A	18-11-93
		CN 1082400 A	23-02-94
		MX 9302203 A	29-04-94
		WO 9320815 A	28-10-93
		US 5364616 A	15-11-94